

Nevoid Basal Cell Carcinoma Syndrome With Medulloblastoma in an African-American Boy: A Rare Case Illustrating Gene-Environment Interaction

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We present an 8-year-old African-American boy with medulloblastoma and nevoid basal cell carcinoma syndrome (NBCCS) who exhibited the radiosensitive response of basal cell carcinoma (BCC) formation in the area irradiated for medulloblastoma. Such a response is well-documented in Caucasian NBCCS patients with medulloblastoma. The proband was diagnosed with medulloblastoma at the age of 2 years and underwent surgery, chemotherapy, and craniospinal irradiation. At the age of 6 years, he was diagnosed with NBCCS following his presentation with a large odontogenic keratocyst of the mandible, pits of the palms and soles and numerous BCCs in the area of the back and neck that had been irradiated previously for medulloblastoma. Examination of other relatives showed that the proband's mother also had NBCCS but was more mildly affected; in particular, she had no BCCs. This case illustrates complex gene-environment interaction, in that increased skin pigmentation in African-Americans is presumably protective against ultraviolet, but not ionizing, radiation. This case and other similar cases in the literature show the importance of considering NBCCS in the differential diagnosis of any patient who presents with a medulloblastoma, especially before the age of 5 years, and of examining other close relatives for signs of NBCCS to

determine the patient's at-risk status. Finally, for individuals who are radiosensitive, protocols that utilize chemotherapy in lieu of radiotherapy should be considered. *Am. J. Med. Genet.* 69:309–314, 1997.

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KEY WORDS: nevoid basal cell carcinoma syndrome (NBCCS); Gorlin syndrome; medulloblastoma; African-Americans, gene-environment interaction; craniospinal irradiation; chemotherapy

INTRODUCTION

Nevoid basal cell carcinoma, or Gorlin, syndrome (NBCCS) [Binkley and Johnson, 1951; Howell and Caro, 1959; Gorlin and Goltz, 1960] is an autosomal dominant disorder with nearly complete penetrance and variable expressivity [Anderson et al., 1967; Howell and Anderson, 1982]. Major clinical findings include multiple basal cell carcinomas (BCCs), odontogenic keratocysts of the jaw, pits of the palms and/or soles, ectopic calcifications (especially of the falx cerebri), and various skeletal anomalies [Gorlin, 1987]. Patients commonly have a characteristic face with increased occipitofrontal circumference, frontal and biparietal bossing, mild hypertelorism, broad nasal root, and mandibular prognathia. Medulloblastoma is occasionally seen in NBCCS.

CLINICAL REPORT

The proband is an 8-year-old African-American boy, born to nonconsanguineous parents. At 18 months,

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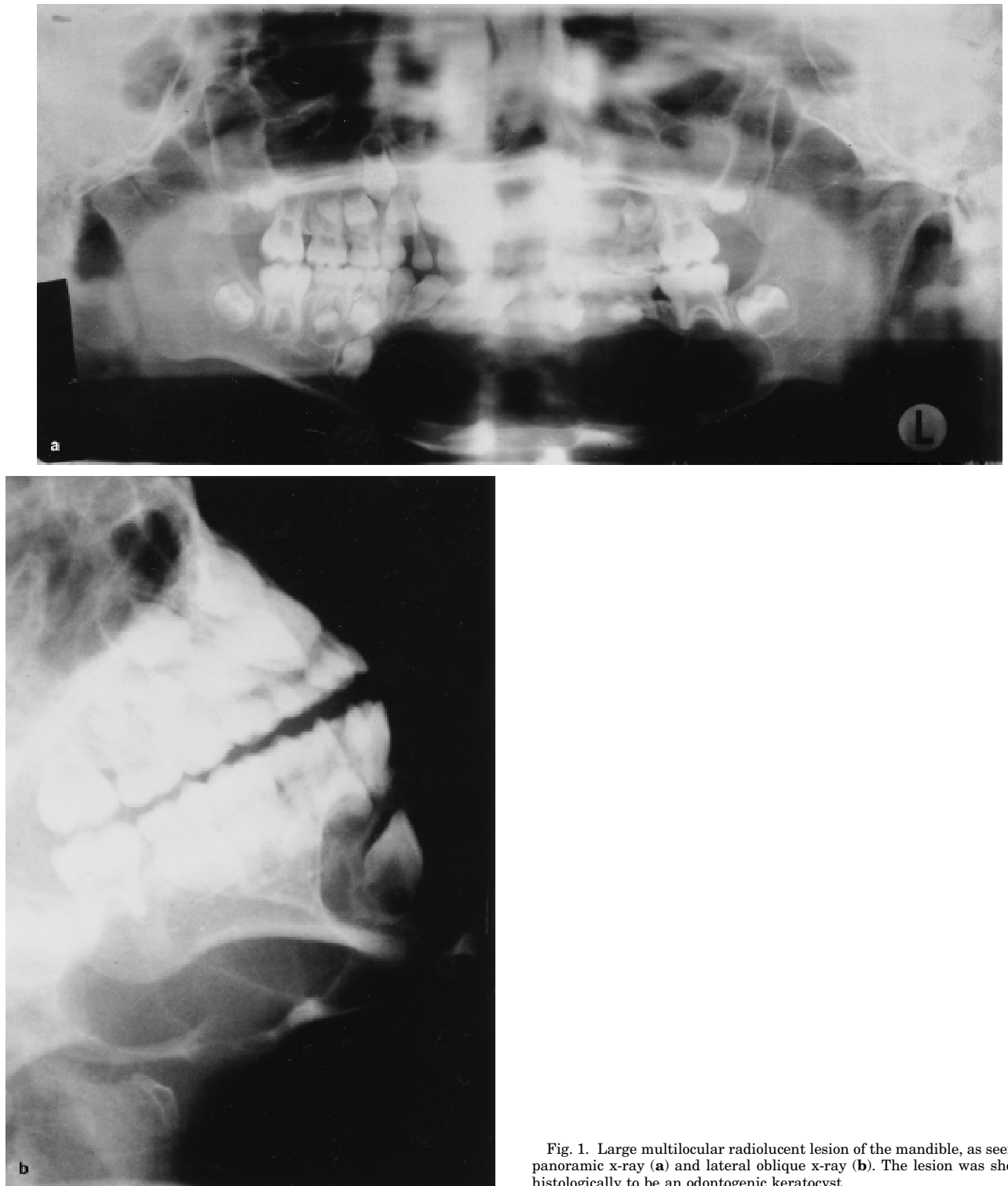


Fig. 1. Large multilocular radiolucent lesion of the mandible, as seen in panoramic x-ray (a) and lateral oblique x-ray (b). The lesion was shown histologically to be an odontogenic keratocyst.

he developed a slowly progressive ataxia of the lower limbs and abnormal eye movements. At the age of 2 years, he was diagnosed with marked hydrocephalus secondary to a very large midline posterior fossa mass. He underwent suboccipital craniectomy with subtotal

resection of the tumor. Multiple subarachnoid metastases were noted along the spinal axis. Pathologic review showed a desmoplastic medulloblastoma with astrocytic differentiation.

Following surgery, the propositus was enrolled in a



Fig. 2. Numerous flesh-tone and hyperpigmented papules [two biopsy-proven basal cell carcinomas (BCCs)] in the zone of previous irradiation for medulloblastoma. View of neck and shoulders from the front (a) and back (b). Note the well-healed scar from the previous craniectomy.

Fig. 3. a: Figure is on overleaf. b: Magnified view of the pits of the left palm in the region of the fifth finger. Many of the pits are hyperpigmented.

Fig. 4. a: Figure is on overleaf. b: Magnified view of the pits of the right heel. Note that both hyperpigmented and flesh-tone pits are present.

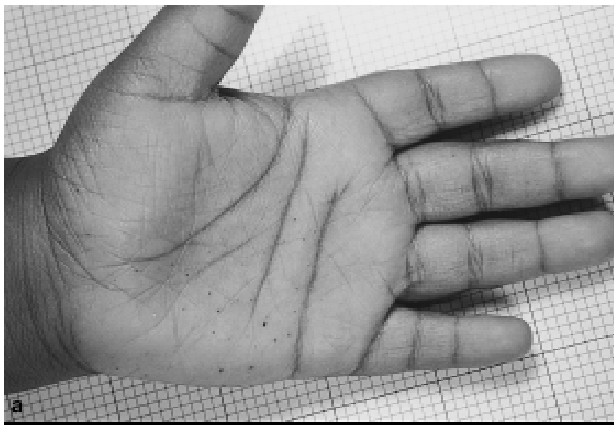


Fig. 3. **a:** Extensive pitting of the left palm.



Fig. 4. **a:** Extensive pitting of the soles.

combined modality protocol at the National Cancer Institute (Bethesda, MD). He received chemotherapy for 51 weeks that consisted of thiotepa, cisplatin, cyclophosphamide, vincristine, and etoposide. This chemotherapy was followed by 6 weeks of daily craniospinal irradiation to a cumulative dose of 3,500 cGy to the whole brain and 5,300 cGy to the posterior fossa. All chemotherapy and radiation therapy were completed by the time the *propositus* was 3.5 years old. Complications that were encountered during treatment included transient hepatic and renal insufficiency, granulocytopenia, thrombocytopenia, and bilateral high-frequency hearing loss due to cisplatin therapy.

At the age of 5.75 years, a lateral x-ray film of the chest showed a possible lytic area in the mandible. Six months later, he had a dental evaluation at the National Institutes of Health for swelling of his gums and jaws and pain while chewing. Several of his lower teeth were displaced or mobile, and there was palpable expansion of the buccal and lingual plates of the mandible. Panoramic and lateral oblique x-ray films showed a multilocular radiolucency of the mandible that extended from the left molar region across the midline to the right primary molar region, displacing a tooth bud (Fig. 1). Biopsy of the lesion demonstrated a

cyst with a squamous-lined wall, keratinaceous debris, and marked inflammation, consistent with an odontogenic keratocyst. No evidence of neoplasm was seen. Forty milliliters of yellow material were removed from the cyst cavity, and gross destruction of the lower jaw was noted. The odontogenic keratocyst was then marsupialized. Four months later, computed tomography scan of the mandible showed healing of the cortical bone, and the cyst was then enucleated.

At the time the *propositus*' odontogenic keratocyst was diagnosed, he was also found to have numerous flesh-tone and hyperpigmented papules in the area of the neck, shoulders, and back that had been irradiated previously for medulloblastoma (Fig. 2). The papules were raised and measured about 1–2 mm in diameter; some appeared pearly, whereas others were polypoid in a shape that was similar to skin tags. In addition, he had extensive pitting of the palms and soles, with many pits being hyperpigmented (Figs. 3, 4). Based on these findings, he was diagnosed with NBCCS. Two representative skin lesions were subsequently biopsied and were shown to be BCCs. Further examination documented that he had a slightly large head circumference, frontal bossing, ocular hypertelorism, and a high-arched palate. X-ray studies did not show lytic or

blastic lesions of the skull, ribs, ankles, heels, feet, or wrists.

At the age of 8 years, the proband developed two new mandibular cysts, each of which contained a tooth. These cysts were enucleated and were found to be multiloculated odontogenic keratocysts, each with an associated odontogenic fibroma. Neither cyst represented a recurrence of the original odontogenic keratocyst. To date, computed tomography scans, magnetic resonance imaging, and lumbar punctures have not shown signs of recurrence of the medulloblastoma.

Following the diagnosis, other relatives were examined. His 4-year-old brother showed no evidence of the syndrome, and the 34-year-old father was found to be unaffected. However, the 38-year-old mother had a large head circumference, a high-arched palate, a mandibular odontogenic keratocyst, impacted and supernumerary teeth, extensive calcification of the falx cerebri and dura mater, and small cystic osteolytic lesions of the tubular bones of the hands, the distal radius, and the ulna. She did not have any BCCs or pits of the palms or soles. No signs of NBCCS were found in any of the other maternal relatives who were examined, including the grandmother, uncle, half-aunt, and half-uncle. The maternal grandfather was unavailable for evaluation.

DISCUSSION

Few published reports on NBCCS patients involve African-Americans [Cotten et al., 1982; Goldstein et al., 1994]. Although these individuals develop BCCs at a much lower frequency (32% with single BCCs, 16% with more than 2 BCCs) [Goldstein et al., 1994] than Caucasians (90% with BCCs; 75% with multiple, early-onset BCCs) [Howell, 1984; Gorlin, 1987], expression of the other components of the disorder is similar in the two groups [Anderson et al., 1967]. Because most NBCCS patients come to clinical attention either because of their BCCs or jaw cysts, African-Americans, in whom BCC expression is relatively rare, are less likely to be ascertained.

Recent studies have estimated the frequency of medulloblastoma in NBCCS patients to be 3–5% [Evans et al., 1993; Kimonis et al., 1997], and NBCCS in medulloblastoma patients is estimated to be approximately 1–2% overall and 4.5% in patients younger than 5 years of age [Evans et al., 1991]. We were able to find only one report of an African-American with both NBCCS and medulloblastoma, a 4-year-old girl who died 1 year after diagnosis of medulloblastoma due to the recurrence of the tumor [Neblett et al., 1971].

Patients with medulloblastoma typically undergo surgery, radiation, and chemotherapy. Those who also have NBCCS often develop numerous BCCs in the irradiated areas, usually 6 months to 3 years following radiotherapy [Strong, 1977]. This BCC response to irradiation occurs much earlier than the median latency period of 21 years for radiation-induced skin cancer in patients without NBCCS [Martin et al., 1970]. However, the only NBCCS patients in whom we were able to find reports of such radiosensitivity were Caucasian. The proband in this study developed many BCCs in

the irradiated area within 3 years of treatment, similar to the latency period observed in Caucasian NBCCS patients. The restriction of BCC development to the previously irradiated area suggests that the skin pigmentation of the proband may be protective against ultraviolet, but not ionizing, radiation.

At the time of diagnosis of medulloblastoma, many NBCCS patients, including the proband, have not yet shown sufficient manifestations to be diagnosed with NBCCS. This is a consequence of the different ages of onset of various traits of NBCCS, e.g., approximately 2 years for medulloblastoma [Evans et al., 1991; Kimonis et al., 1997] vs. 15 and 20 years for jaw cysts and BCCs, respectively [Anderson et al., 1967; Shanley et al., 1994; Kimonis et al., 1997]. Any patient who presents with medulloblastoma at an unusually young age should be evaluated for NBCCS, because the mean age of onset of medulloblastoma in NBCCS is younger than in the general population, 2 years vs. 6–10 years, respectively [Neblett et al., 1971; Evans et al., 1991]. This evaluation should include examination of other close relatives who have attained an age at which clinical findings of NBCCS are more likely. For those medulloblastoma patients who are determined to have or to be at risk of having NBCCS, treatments other than radiotherapy should be utilized if possible [Howell and Anderson, 1982; Evans et al., 1991].

The NBCCS locus was mapped to chromosome 9q22.3 [Farndon et al., 1992; Gailani et al., 1992; Reis et al., 1992]. Familial and sporadic BCCs [Gailani et al., 1992; Chenevix-Trench et al., 1993; Bonifas et al., 1994], medulloblastomas [Albrecht et al., 1994; Schofield et al., 1995], jaw cysts [Levanat et al., 1996], and ovarian fibromas [Gailani et al., 1992] showed loss of heterozygosity in this region, suggesting that the gene functions as a tumor suppressor. Recently, alterations in the human homolog (*PTC*) of the *Drosophila* segment polarity gene *patched* (*ptc*) were identified in NBCCS patients as well as tumors associated with the syndrome [Hahn et al., 1996a,b; Johnson et al., 1996]. Although a minimum of two hits may be necessary for tumorigenesis in NBCCS, it is likely that additional genetically and environmentally mediated events are required for full expression of the syndrome.

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